510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

K113200

B. Purpose for Submission:

Substantial equivalence determination for a change in antimicrobial concentrations and a modification of the formulation of Piperacillin/tazobactam to the VITEK® 2 and VITEK®2 Compact Systems Antimicrobial Susceptibility Test (AST) System.

C. Measurand

VITEK® 2 Gram Negative Piperacillin/tazobactam (≤ 4- ≥ 128 µg/ml)

D. Type of Test:

Quantitative growth based detection algorithm using optics light detection

E. Applicant:

bioMerieux, Inc.

F. Proprietary and Established Names:

Vitek®2 Gram Negative Piperacillin/tazobactam

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
LON	Class II	21 CFR 866.1645	83, Microbiology

H. Intended Use:

1. Intended use(s):

   VITEK® 2 Gram Negative Piperacillin/tazobactam is designed for antimicrobial susceptibility testing of Gram negative bacilli and is intended for use with the VITEK® 2 and VITEK 2 Compact Systems as a laboratory aid in the determination of in vitro susceptibility to antimicrobial agents. VITEK 2 Gram Negative Piperacillin/tazobactam is a qualitative test.

Piperacillin/tazobactam has been shown to be active against the microorganisms listed below, according to the FDA label for this antimicrobial.

Active in vitro and in clinical infections
Acinetobacter baumannii, Klebsiella pneumoniae, Escherichia coli Pseudomonas aeruginosa (given in combination with an aminoglycoside to which the isolate is susceptible)

In vitro data available but clinical significance is unknown
Citrobacter koseri, Proteus vulgaris, Morganella morganii, Providencia stuartii, Proteus mirabilis, Providencia rettgeri, Salmonella enterica

2. Indication(s) for use:

VITEK® 2 Gram Negative Piperacillin/tazobactam is designed for antimicrobial susceptibility testing of Gram negative bacilli and is intended for use with the VITEK® 2 and VITEK 2 Compact Systems as a laboratory aid in the determination of in vitro susceptibility to antimicrobial agents. VITEK 2 Gram Negative Piperacillin/tazobactam is a qualitative test. Piperacillin/tazobactam has been shown to be active against the microorganisms listed below, according to the FDA label for this antimicrobial.

Active in vitro and in clinical infections
Acinetobacter baumannii, *Klebsiella pneumoniae*, *Escherichia coli Pseudomonas aeruginosa* (given in combination with an aminoglycoside to which the isolate is susceptible)

In vitro data available but clinical significance is unknown
Citrobacter koseri, *Proteus vulgaris*, *Morganella morganii*, *Providencia stuartii*, *Proteus mirabilis*, *Providencia rettgeri*, *Salmonella enterica*

The VITEK® 2 Antimicrobial Susceptibility Test (AST) is intended to be used with the VITEK® 2 Systems for the automated quantitative or qualitative susceptibility testing of isolated colonies for the most clinically significant aerobic gram-negative bacilli, *Staphylococcus* spp., *Enterococcus* spp., *Streptococcus* spp. and clinically significant yeast.

3. Special condition for use statement(s):

Prescription Use Only.

Perform an alternative method of testing prior to reporting of results when a resistant result is obtained with the following antibiotic/organism combination(s): Piperacillin/Tazobactam and *P. aeruginosa*

4. Special instrument Requirements:

For use with the VITEK® 2 and VITEK® 2 Compact Systems

I. Device Description:

The VITEK® 2 AST card containing the test is inoculated with a standardized organism suspension. The card is incubated within the instrument and optically monitored throughout the incubation cycle. Results are automatically calculated once a predetermined growth threshold is reached and a report is generated that contains the final result.

J. Substantial Equivalence Information:

1. Predicate device name(s):

VITEK® 2 Gram Negative Meropenem

2. Predicate K number(s):

K091899

3. Comparison with predicate

Similarities		
Item	Device	Predicate
Intended Use	Determining susceptibility to antimicrobial agents	Same
Inoculation and test organism	Isolated colonies of Gram negative bacilli	Same
Instrument	Test are run on both the VITEK 2 and VITEK 2 Compact Systems	Same
Test Card	The VITEK 2 card	Same

Differences		
Item	Device	Predicate
Test Method	Automated **qualitative** antimicrobial susceptibility test for use with the VITEK® 2 and	Automated **quantitative** antimicrobial susceptibility test for use with the VITEK® 2 and

Differences		
Item	Device	Predicate
	VITEK® 2 Compact Systems to determine the *in vitro* susceptibility of Gram negative bacilli	VITEK® 2 Compact Systems to determine the *in vitro* susceptibility of Gram negative bacilli
Antibiotic	Piperacillin/tazobactam	Meropenem
Reading algorithm	Unique for new formulation of Piperacillin/tazobactam	Unique for Meropenem
Test concentrations on the card	Piperacillin/tazobactam: 2/4, 8/4, 24/4, 32/4, 32/8, and 48/8 µg/mL for a calling range of ≤4 - ≥128 µg/mL	Meropenem: 0.25, 0.5, 1, and 4 µg/mL for a calling range of ≤0.12 - ≥8µg/mL

K. Standard/Guidance Document Referenced (if applicable):

Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA.

Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard -7th Edition, Document M7-A8.

Performance Standards for Antimicrobial Susceptibility Testing – 19th Informational Supplement, M100-S19.

L. Test Principle:

Each VITEK® 2 test card contains 64 microwells. A control well, that contains only microbiological culture medium is resident on all cards, with the remaining wells containing premeasured amounts of a specific antibiotic combined with culture medium. A suspension of organism is made in 0.45-0.5% sterile saline from a pure culture and standardized to a McFarland 0.5 standard using the DensiChek. The desired card(s) are placed in the cassette along with an empty tube for the susceptibility card. The cassette is placed in the VITEK® 2 instrument where a susceptibility test will be automatically diluted from the ID suspension by the VITEK® 2. The cards are then automatically vacuum filled; the tubes are cut and the cards sealed prior to proceeding to the Incubator Loading Station. Cards are then transferred from the cassette into the carousel for incubation (35.5^{o} C) and optical scanning during testing. Readings are performed every 15 minutes.

In addition to the automatic dilution, there is also a manual inoculation dilution procedure described in the packager insert.

M. Performance Characteristics (if/when applicable):

Studies were conducted to evaluate a new Piperacillin/tazobactam susceptibility panel, tzp03n, which contains new media formulation and different drug concentrations from the original test panels. This modification was made to address a Class I recall of the previous product (tzp02n) which was on the market.

1. Analytical performance:

    a. *Precision/Reproducibility:*

    Reproducibility was demonstrated using 10 isolates at three sites on three separate days in triplicates. The study included the Auto-dilution and the Manual dilution for VITEK 2 and Manual dilution for VITEK 2 Compact. The majority of the MIC values were on-scale.

    For reproducibility calculations, off-scale values are handled in two ways; "best case" and "worst case" scenarios. Best case calculation for reproducibility assumes the off-scale result is within one well from the mode MIC value. Worst case calculation for reproducibility assuming the off-scale result is greater than one well from the mode MIC value.

    The overall reproducibility was >95% with +/- one dilution observation for all three methods. For Automatic Dilution, the VITEK 2 Gram Negative Piperacillin/tazobactam gave overall reproducibility values of 96.7% and 88.9% based on best case and worst case calculations, respectively. For Manual Dilution, the VITEK 2 Gram Negative Piperacillin/tazobactam gave overall reproducibility values of 95.9% and 90.0% based on best case and worst case calculations, respectively.

    A similar reproducibility study was conducted by testing on the VITEK 2 Compact instrument. The VITEK 2 Gram Negative Piperacillin/tazobactam gave overall reproducibility values of 99.5% and 97.2% based on best case and worst case calculations, respectively. Only Manual Dilution testing was conducted since the VITEK 2 Compact system does not have a functionality to support automatic dilution to inoculate the card.

    b. *Linearity/assay reportable range:*

    Not Applicable

c. Traceability (controls, calibrators, or method):

Three recommended QC (*E. coli* ATCC 25922, *E. coli* ATCC 35218 and *P. aeruginosa* ATCC 27853) were tested a minimum 20 times/site by the automatic dilution and the manual dilution. The organisms were tested by the VITEK 2 AST cards and the reference (broth microdilution) methods.

Both the Auto dilution and the Manual dilution methods are within the expected range >95% of the time. The Reference Results are similar to the test results. In instances where any organism was out of range for the reference method, all testing data was invalid and repeated.

The following table provides the frequency of results for all sites in each concentration with the expected range stated. The Reference method results produced QC results that are on scale and within the expected QC ranges for all organisms 100% of the time.
The QC results obtained with the VITEK 2 Gram Negative Piperacillin/tazobactam are not on-scale because the calling range (≤4 - ≥128 µg/mL) does not cover the low end of the expected MIC values for any of the recommended QC strains. Although the QC strains selected had ranges at the lower end, that were reflected in the Reference test, the VITEK system could not detect variations at the low end of the MIC range using these three QC strains. However, these QC strains will allow detection of trends at the high end of the QC range, such as would occur in cases of degradation of the drug.

Organism	Conc in µg/ml	Auto-dilution		Manual dilution	
E. coli ATCC 25922 Range 1- 4 µg/ml		**Ref.**	**Test**	**Ref.**	**Test**
	≤ 0.125				
	0.25				
	0.5				
	1	15		15	
	2	92		92	
	4	27		27	
	≤ 4*		134		132
	8*				
	16*				
	32*				
	64*				1
	128*				1
	≥256				

Organism	Conc in µg/ml	Auto-dilution		Manual dilution	
E. coli ATCC 35218 Range 0.5- 2 µg/ml	≤ 0.125				
	0.25				
	0.5				
	1	77		76	
	2	55		55	
	4	1		1	
	≤ 4*		132		130
	8*				
	16*				
	32*				
	64*				
	128*		1		2
	≥256				
P. aeruginosa ATCC 27853 Range 1- 8 µg/ml	≤ 0.125				
	0.25				
	0.5				
	1				
	2	9		9	
	4	135		113	
	≤ 4*		132		129
	8*	9		9	
	16*	1			
	32*				
	64*				
	128*		2		3
	≥256				

* The VITEK calling range is (≤4 - ≥128 µg/mL).

Inoculum density control:

A turbidity meter (VITEK 2 DensiChek) was used to adjust the inoculum to the turbidity of 0.5 McFarland. The VITEK 2 DensiChek instrument was standardized weekly with all results recorded and in the expected range. Verification was performed during internal testing.

d. Detection limit:
Not Applicable

e. Analytical specificity:
Not Applicable

f. Assay cut-off:
Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

A clinical study was performed at three external sites using the VITEK 2 AST-GN Piperacillin/tazobactam and broth microdilution panels containing Piperacillin/tazobactam. The study included 2358 clinical isolates (1253 clinical isolates and 1105 additional surveillance isolates-referred to as "expanded" panel were tested as part of evaluating the new formulation, tz03n) and a challenge set of 95 isolates. The expanded surveillance study data was combined with the original clinical trial data set. Therefore, performance is based on the combined data set of 2453 (clinical, surveillance and challenge isolates). Stock isolates were approximately 28% of all clinical isolates.

Two methods of inoculation (manual and automated) were evaluated. Clinical testing was performed by the automated method of inoculation and the challenge set was by both the manual and the automated methods. All isolates grew in the VITEK®2 cards in less than 16 hours.

The test device had a growth rate of >95% for the clinical and the challenge study. Overall, there were 5 very major errors (0.8% error rate, 5/565 resistant isolates), 40 major errors (2.1% error rate, 40/1888 susceptible isolates), and 123 minor errors. These overall error rates are acceptable (see separate analysis for *P. aeruginosa*, since a large number of the major error rates occurred with this organism).

Combined Performance Summary for Indicated *Enterobacteriaceae* species, *P. aeruginosa*, and *Acinetobacter baumannii* **(Auto Dilution)**

	Total	EA	%EA	Eval EA Total	Eval EA	Eval %EA	CA	%CA	#R	vmj	maj	min
Clinical	**1253**	**1181**	**94.3**	**182**	**142**	**78.0**	**1182**	**94.3**	**160**	**0**	**22**	**49**
Challenge	**95**	**91**	**95.8**	**38**	**34**	**89.5**	**91**	**95.8**	**17**	**0**	**1**	**3**
Expanded	**1105**	**1033**	**93.5**	**128**	**83**	**64.8**	**1012**	**91.6**	**388**	**5**	**17**	**71**
Combined	**2453**	**2305**	**94.0**	**348**	**259**	**74.4**	**2285**	**93.2**	**565**	**5**	**40**	**123**

EA-Essential Agreement
CA-Category Agreement
R-resistant isolates
maj-major discrepancies
vmj-very major discrepancies
min- minor discrepancies

Performance Summary for *P. aeruginosa*

	Total	EA	%EA	Eval EA Total	Eval EA	Eval %EA	CA	%CA	#R	vmj	maj	min
Clinical	168	155	92.3	68	62	91.2	156	92.9	44	0	12	0
Challenge	19	19	100.0	12	12	100.0	18	94.7	2	0	1	0
Expanded	106	98	92.5	19	13	68.4	93	87.7	65	2	11	0
Combined	293	272	92.8	99	87	87.9	267	91.1	111	2	24	0

For *P. aeruginosa*, there were 24 major errors observed among 182 isolates classified as susceptible. This represents a major error rate of 13.1%, which does not meet the acceptable criteria of ≤3%. Since there is no intermediate category in the susceptibility interpretative criteria for *P. aeruginosa* discrepant results are either very major error (vmj) or a major error (maj).

This high major error rate for *P. aeruginosa* indicates that a false resistance call occurred at an unacceptable rate. Based on this performance, and in order to avoid reporting of false resistance to this drug, the package insert will include a limitation instructing the user to perform an alternative method when a resistant results is obtained with Piperacillin/tazobactam when testing *P. aeruginosa*.

Manual Dilution:
The challenge set of 95 organisms was also tested at one site using the manual method of inoculation with the following performance. There was no difference in the overall CA agreement.

Comparison Challenge Data - Auto vs Manual dilution

	total	EA	%EA	Eval EA Total	Eval EA	Eval %EA	CA	%CA	#R	vmj	maj	min
Auto	95	91	95.8%	38	34	89.5%	91	95.8%	17	0	1	3
Manual	95	88	92.6%	39	35	89.7%	89	93.7%	17	0	2	4

b. Matrix comparison:
Not Applicable

3. Clinical studies:
   a. Clinical sensitivity:
   Not Applicable

   b. Clinical specificity:
   Not Applicable

   c. Other clinical supportive data (when a and b are not applicable):

4. Clinical cut-off:

   Not Applicable

5. Expected values/Reference range

   The interpretative criteria and the recommended Quality Control ranges are the same as the FDA approved drug label and Clinical and Laboratory Standards Institute (CLSI) standards and will appear in the Package Insert and software. Interpretative criteria used for the evaluation and that will appear in the Package Insert are as follows:

   Enterobacteriaceae and *Acinetobacter baumanii*

≤ 16 (S)	32-64 (I)	≥ 128 (R)

   Pseudomonas aeruginosa

≤ 64 (S)	----	≥ 128 (R)

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR section 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.